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HYBRID SIMULATION TECHNIQUE FOR PATIENT CONTROLLED ANALGESIA USING REAL PATIENT DATA

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ABSTRACT

In this paper we assume that the patient's demand in patient controlled analgesia (PCA) is a random process with a unique shape and parameters. In order to find this process we investigated two randomly selected, real data based morphine and fentanyl PCA logs and created patients' behavioral model that approximated real demand data.

We used the created patient behavioral models to create 500 virtual PCA logs of both morphine and fentanyl analgesia. These logs allowed pharmacokinetic simulation of the effect compartment concentration. We used quantized state system model to create hybrid aggregate model of PCA. The proposed methodology allows an estimation of frequency and duration of critical episodes during PCA.

1 HYBRID AGGREGATE MODEL OF PCA

For simulation of patient controlled analgesia we used hybrid systems simulation method based on PLA formalism (Pranevicius et al. 1991).

PLA is a special case of automaton models. In the application of the PLA approach for system specification, the system is represented as a set of interacting piece-linear aggregates. The PLA is taken as an object defined by a set of states *Z*, input signals *X*, and output signals *Y*. Behavior of an aggregate is considered in a set of time moments $t \in T$. States $z \in Z$, input signals $x \in X$, and output signals $y \in Y$ are considered to be time functions. Transition and output operators, *H* and *G* correspondingly, must be known as well.

For hybrid aggregate model (Pranevicius et al. 2011) continuous coordinates model is described by the system of ordinary differential equations (ODEs). To solve the system of ODEs we have adopted Quantized State System (QSS) method, which was defined in (Kofman 2004). QSS method was implemented using PLASim simulation library, which was created in our department.

2 PATIENTS' BEHAVIORAL MODEL

We used two random real data logs from PCA device, one with a prescription for morphine and one for fentanyl. We analyzed the length of time period (in minutes) between the two consecutive drug requirements. SPSS and MATLAB statistical tools were used to fit suitable models.

Analysis of morphine PCA demands. We compared 25 different ARMA(*p*,*q*) models, with values of *p* and *q* ranging from 0 to 4, and chose the model with the lowest value of Bayesian Information Criterion (BIC). The ARMA(0,0) model with linear trend had the lowest BIC value for morphine analgesia. The following model was chosen: $y_t = 21.029 + \varepsilon_t$, where ε has exponential distribution.

Analysis of fentanyl PCA demands. The ARMA(2,0) model with linear trend had the lowest BIC value for fentanyl analgesia. The model equation with estimated model parameters is as follows:

$y_t = 11{,}57 + 0{,}264t - 0{,}302y_{t-1} + 0{,}203y_{t-2} + \varepsilon_t$, where ε_t has the generalized extreme values distribution.

3 SIMULATION OF PCA

A three compartmental model of drug distribution between the serum and the brain tissue (effect compartment) was used to describe fentanyl and morphine pharmacokinetics/pharmacodynamics. Morphine and fentanyl micro rate constants were chosen from (Dahlstrom et al. 1990) and (Shafer et al. 1990).

For the evaluation of critical periods during PCA we generated 500 patients demand logs and used hybrid simulation technique to estimate drug plasma and effect compartment concentrations according to the pharmacokinetic multi-compartmental models. Increased risk event was defined as the time when effect compartment concentration exceeded critical (toxic) threshold. From that, cumulative risk could be defined as the time above this threshold and may correlate with the duration and severity of respiratory depression.

500 simulation sessions were performed, that modeled morphine and fentanyl concentrations at the effect site during 24 hours period. Simulation was performed by using personal patients' behavioral model together with pharmacokinetic compartmental models. Two parameters were evaluated: the number of times critical concentration threshold was exceeded during 24 hours simulation period and the duration of the periods when concentration exceeds critical threshold.

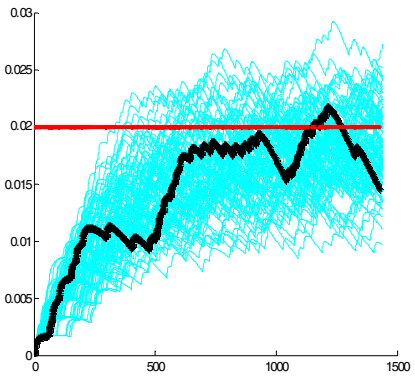

Figure 1: The comparison of estimated patients' drug concentration at the effect site (bold line) using 500 simulated morphine PCA logs (critical threshold 0.02)

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